BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images, please do not report the images to the Image Problem Mailbox.

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61L 15/44 — A1

(11) International Publication Number: **WO 97/24148**

(43) International Publication Date: 10 July 1997 (10.07.97)

(21) International Application Number: PCT/US96/20365

(22) International Filing Date: 27 December 1996 (27.12.96)

(30) Priority Data:
08/583,523 29 December 1995 (29.12.95) US

(71) Applicant: CYGNUS, INC. [US/US]; 400 Penobscot Drive, Redwood City, CA 94063 (US).

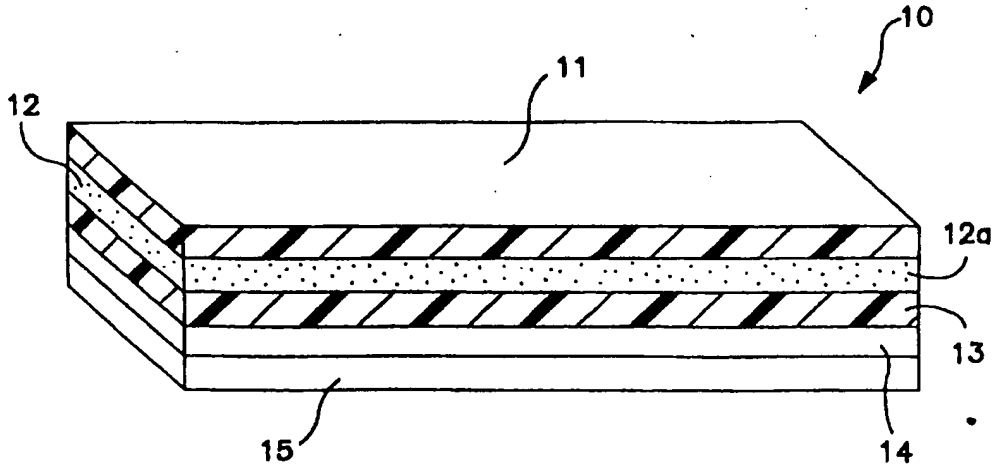
(72) Inventors: CHEN, Tung-Fen; 1674 Hollenbeck Avenue #20, Sunnyvale, CA 94087 (US). CHIANG, Chia-Ming; 380 Shad Court, Foster City, CA 94404 (US). JONA, Janan; 125 Connemara Way #168, Sunnyvale, CA 94087 (US). JOSHI, Priti; 5919 Royal Ann Drive, San Jose, CA 95129 (US). RAMDAS, Asha; 707 Continental Circle #326, Mountain View, CA 94040 (US).

(74) Agents: REED, Dianne, E.; Reed & Robins L.L.P., Suite 200, 285 Hamilton Avenue, Palo Alto, CA 94301 (US) et al.

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: SYSTEMS AND METHODS FOR THE TRANSDERMAL ADMINISTRATION OF ANDROGENIC AGENTS



(57) Abstract

Drug delivery systems and methods for transdermally administering androgenic agents are provided. The systems are generally laminated composites containing a pharmaceutical formulation within a drug reservoir, wherein an androgenic agent is present in the formulation at or above saturation concentration. The composite is also provided with a means for adhering to the skin or mucosal tissue. The reservoirs are typically comprised of "high capacity" materials such as polyurethane hydrogels or superabsorbent materials. The androgenic agent will in most cases be testosterone or a pharmaceutically acceptable derivative thereof, administered alone or in combination with an estrogen and/or progestogen.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia
AT	Austria
AU	Australia
BB	Barbados
BE	Belgium
BF	Burkina Faso
BG	Bulgaria
BJ	Benin
BR	Brazil
BY	Belarus
CA	Canada
CF	Central African Republic
CG	Congo
CH	Switzerland
CI	Côte d'Ivoire
CM	Cameroon
CN	China
CS	Czechoslovakia
CZ	Czech Republic
DE	Germany
DK	Denmark
EE	Estonia
ES	Spain
FI	Finland
FR	France
GA	Gabon
GB	United Kingdom
GE	Georgia
GN	Guinea
GR	Greece
HU	Hungary
IE	Ireland
IT	Italy
JP	Japan
KE	Kenya
KG	Kyrgystan
KP	Democratic People's Republic of Korea
KR	Republic of Korea
KZ	Kazakhstan
LI	Liechtenstein
LK	Sri Lanka
LR	Liberia
LT	Lithuania
LU	Luxembourg
LV	Latvia
MC	Monaco
MD	Republic of Moldova
MG	Madagascar
ML	Mali
MN	Mongolia
MR	Mauritania
MW	Malawi
MX	Mexico
NE	Niger
NL	Netherlands
NO	Norway
NZ	New Zealand
PL	Poland
PT	Portugal
RO	Romania
RU	Russian Federation
SD	Sudan
SE	Sweden
SG	Singapore
SI	Slovenia
SK	Slovakia
SN	Senegal
SZ	Swaziland
TD	Chad
TG	Togo
TJ	Tajikistan
TT	Trinidad and Tobago
UA	Ukraine
UG	Uganda
US	United States of America
UZ	Uzbekistan
VN	Viet Nam

SYSTEMS AND METHODS FOR THE TRANSDERMAL ADMINISTRATION OF ANDROGENIC AGENTS

Technical Field

This invention relates generally to transdermal drug delivery, and more particularly relates to methods and drug delivery systems for administering androgenic agents transdermally. The invention additionally relates to high capacity drug reservoirs useful in conjunction with the transdermal administration of androgenic agents as provided herein.

Background

The delivery of drugs through the skin provides many advantages; primarily, such a means of delivery is a comfortable, convenient and noninvasive way of administering drugs. The variable rates of absorption and metabolism encountered in oral treatment are avoided, and other inherent inconveniences -- e.g., gastro-intestinal irritation and the like -- are eliminated as well. Transdermal drug delivery also makes possible a high degree of control over blood concentrations of any particular drug.

Skin is a structurally complex, relatively thick membrane. Molecules moving from the environment into and through intact skin must first penetrate the stratum corneum. They must then penetrate the viable epidermis, the papillary dermis, and the capillary walls into the blood stream or lymph channels. To be so absorbed, molecules must overcome a different resistance to penetration in each type of tissue. Transport across the skin membrane is thus a complex phenomenon. However, it is the cells of the stratum corneum which present the primary barrier to absorption of topical compositions or transdermally administered drugs. The stratum corneum is a thin layer of dense, highly keratinized cells approximately 10-15 microns thick

over most of the body. It is believed to be the high degree of keratinization within these cells as well as their dense packing which creates in most cases a substantially impermeable barrier to drug penetration.

Relatively recent advances in transdermal drug delivery have enabled effective administration of a variety of drugs through the skin. These advances include the development of a number of skin penetration enhancing agents, or "permeation enhancers," to increase skin permeability, as well as non-chemical modes for facilitating transdermal delivery, e.g., the use of iontophoresis, electroporation or ultrasound. Nevertheless, the number of drugs that can be safely and effectively administered through the skin, without concomitant problems such as irritation or sensitization, remains limited.

The present invention is directed to the transdermal administration of certain androgenic agents. Particular compounds of interest are testosterone and pharmaceutically acceptable esters and derivatives thereof. Such agents are useful in a variety of applications, e.g., in treating hypogonadism, hypopituitarism, Addison's disease, impotence, male infertility disorders, anemia, and in male hormone replacement therapy. The present invention also involves the transdermal administration of androgenic agents in combination with estrogens, in treating, for example, menopause, osteoporosis, or other conditions for which estrogen-androgen combination therapy is indicated.

Transdermal delivery of androgens, alone or in combination with estrogenic agents, has been disclosed. *See, e.g.*, U.S. Patent No. 4,704,282 to Campbell et al., U.S. Patent No. 4,867,982 to Campbell et al., U.S. Patent No. 5,094,857 to Luderschmidt, U.S. Patent No. 5,152,997 to Ebert et al., U.S. Patent No. 5,460,820 to Ebert et al., and PCT Publication No. WO95/03764. The advantage of administering these drugs transdermally are many: there is no first-pass effect; gastrointestinal and other side effects are substantially avoided; continuous delivery provides for sustained blood levels of drug; a transdermal patch is easily removable if any side effects do occur; and the likelihood of patient acceptance is much improved.

None of the art of which applicants are aware describes a transdermal drug delivery system as now provided herein. In contrast to prior systems for administering these drugs transdermally, the present invention is directed to pharmaceutical formulations in which the androgenic agent is present at or above saturation, preferably using transdermal delivery systems having drug reservoirs into which a far greater quantity of drug may be loaded than possible with conventional transdermal systems, in turn enabling delivery of greater quantities of drug, at higher fluxes. In addition, the aforementioned high capacity drug reservoirs may reduce or in some cases eliminate the need for skin permeation enhancers. Further, smaller transdermal patches may be made using such technology, i.e., patches that are at least as effective as prior patches in terms of overall drug release and drug flux, but are significantly reduced in terms of size.

Disclosure of the Invention

Accordingly, the present invention provides drug delivery systems, drug reservoirs, and methods for administering androgenic agents transdermally.

In one aspect of the invention, a selected androgenic agent is administered transdermally using a drug delivery system in which the androgenic agent is present in a pharmaceutical formulation contained within a drug reservoir, and wherein the androgenic agent is present in the formulation at or above saturation. Preferably, the drug reservoir is a high capacity drug reservoir, typically comprised of a polymeric hydrogel or a superabsorbent material. Administration is conducted for a time period and at an administration rate effective to provide the necessary therapy, e.g., treatment of hypogonadism, impotence, infertility disorders, or in male hormone replacement therapy or the like. The method is premised on the discovery that high capacity drug reservoirs may be used to provide relatively small transdermal patches, on the order of 30 cm^2 or smaller, while still achieving a drug flux that is for all contemplated indications more than sufficient.

Optimally, the patches of the invention are designed to be worn for 24-hour periods.

In another aspect of the invention, transdermal drug delivery systems are provided for administering an androgenic agent. The systems may take any number of forms, but are generally laminated composites comprised of a backing layer and a drug reservoir containing the pharmaceutical formulation. As explained above, the androgenic agent is present in the pharmaceutical formulation at or above saturation. The reservoir is preferably a high capacity drug reservoir as alluded to above. The systems also include a means for affixing the composite to the skin, typically either an "in-line" contact adhesive present as a layer underlying the entire surface of the device, or a peripheral adhesive ring. The drug reservoir and the affixing means will typically although not necessarily be physically distinct, such that a separate contact adhesive layer is provided which serves as the basal surface of the device that adheres to the body surface during use. Other components may be present in these transdermal systems as well, including additional adhesive layers and/or reservoirs, rate-controlling membranes, and the like.

In a further aspect of the invention, high capacity drug reservoirs are provided containing a selected androgenic agent. The reservoirs will comprise either polymeric hydrogel matrices, typically polyurethane hydrogels, or matrices formed from superabsorbent materials, usually crosslinked polymers which are capable of absorbing far more than their own weight, typically at least 50 grams liquid per gram polymer.

Brief Description of the Drawings

FIG. 1 is a schematic illustration of one type of transdermal drug delivery system that may be used in conjunction with the present invention.

FIG. 2 is a schematic illustration of an alternative type of transdermal drug delivery system that may be used in conjunction with the present invention.

FIGS. 3 and 4 represent in graph form the skin flux of testosterone obtained using various vehicles, as evaluated in the experimental section herein.

FIG. 5 represents in graph form the cumulative permeation of testosterone obtained using various vehicles, also as evaluated in the experimental section herein.

FIG. 6 represents in graph form the skin flux profiles from various platforms, also as evaluated in the experimental section herein.

FIG. 7 represents in graph form the cumulative permeation of testosterone from various platforms, also as evaluated in the experimental section herein.

Modes for Carrying Out the Invention

Before describing the present invention in detail, it is to be understood that this invention is not limited to particular formulations or transdermal systems as such may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting.

It must be noted that, as used in this specification and the appended claims, the singular forms "a", "an" and "the" include plural referents unless the content clearly dictates otherwise. Thus, for example, reference to "an androgenic agent" includes a mixture of two or more androgenic agents, reference to "an estrogen" or "a progestogen" includes reference to two or more such agents, reference to "an excipient" or "a vehicle" includes mixtures of excipients or vehicles, reference to "a permeation enhancer" includes reference to two or more permeation enhancers, and the like.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which the invention pertains. Although any methods and materials similar or equivalent to those described herein can be used in the practice for testing of the present invention, the preferred materials and methods are described herein.

In describing and claiming the present invention, the following terminology will be used in accordance with the definitions set out below.

The "transdermal" delivery is used herein to encompass not only transdermal (or "percutaneous") drug delivery but also transmucosal administration. That is, "transdermal" delivery intends delivery by passage of a drug through the skin or mucosal tissue into the bloodstream.

By "therapeutically effective" amount is meant a nontoxic but sufficient amount of a compound to provide the desired therapeutic effect, in the present case, that dose of androgenic agent which will be effective in treating the indication at issue. An "effective" amount of a permeation enhancer as used herein means an amount that will provide the desired increase in skin permeability and, correspondingly, the desired depth of penetration, rate of administration, and amount of drug delivered.

By the term "saturated" is meant a pharmaceutical formulation in which the drug is present at saturation; in the context of the present invention, the androgenic agent is present in the pharmaceutical formulation contained in the drug reservoir at or above saturation.

By "predetermined area of skin" is intended a defined area of intact unbroken living skin or mucosal tissue. That area will usually be in the range of about 5 cm^2 to about 40 cm^2, more usually in the range of about 20 cm^2 to about 30 cm^2. However, it will be appreciated by those skilled in the art of transdermal drug delivery that the area of skin or mucosal tissue through which drug is administered may vary significantly, depending on patch configuration, dose, and the like. As noted elsewhere herein, it is

desired that the area of the present delivery systems be on the order of 30 cm^2 or less.

"Penetration enhancement" or "permeation enhancement" as used herein relates to an increase in the permeability of skin to a pharmacologically active agent, i.e., so as to increase the rate at which the drug permeates through the skin and enters the bloodstream. The enhanced permeation effected through the use of such enhancers can be observed by measuring the rate of diffusion of drug through animal or human skin using a diffusion cell apparatus as described in the Examples herein.

"Carriers" or "vehicles" as used herein refer to carrier materials suitable for transdermal drug administration, and include any such materials known in the art, e.g., any liquid, gel, solvent, liquid diluent, solubilizer, or the like, which is nontoxic and which does not interact with other components of the composition in a deleterious manner. Examples of suitable carriers for use herein include water, silicone, liquid sugars, waxes, petroleum jelly, and a variety of other materials. The term "carrier" or "vehicle" as used herein may also refer to stabilizers, crystallization inhibitors, or other types of additives useful for facilitating transdermal drug delivery.

By "high capacity" drug reservoirs, as used herein, is meant systems or reservoirs containing a amount of drug or drug formulation which is greater than that which is typically possible using conventional manufacturing techniques or transdermal drug delivery devices; the drug reservoirs herein can be made so as to contain on the order of 70 wt.% drug formulation or more.

The term "hydrogel" is used in its conventional sense to refer to a water-swellable polymeric matrix in which a dispersed, polymeric phase has combined with a continuous, aqueous phase to form a viscous, colloidal product.

The term "urethane" is used herein in its conventional sense to denote organic compounds containing a recurring -O-(CO)-NH- linkage. The

term "polyurethane" is intended to mean a polymer containing a plurality of urethane units as just defined.

By a "superabsorbent" material, as used herein, is intended a material capable of absorbing or adsorbing an amount of fluid therein corresponding to more than 15 grams, preferably more than 25 grams, most preferably more than 50 grams, per gram of superabsorbent material. Superabsorbent materials are known that are capable of absorbing or adsorbing 300 to 1000 times their weight in fluids as well. Typically, superabsorbent materials are crosslinked polymers. Such superabsorbent materials not only absorb or adsorb fluid but also retain fluid while remaining generally insoluble therein.

The present method of transdermally delivering an androgenic agent may vary, but necessarily involves application to the body surface of a transdermal drug delivery system having the androgenic agent present at or above saturation in a pharmaceutical formulation contained within a drug reservoir, typically and preferably a high capacity drug reservoir. The "body surface" is normally, although not necessarily, nonscrotal skin. The delivery system is affixed to the body surface and retained in place for a period of time sufficient to provide an effective blood level of drug for a desired period of time. Ideally, for treatment of male testosterone insufficiency, the androgenic agent should be delivered at a dosage of at least about 3 mg/day, more preferably at least about 6 mg/day. To achieve such a dosage from a patch of 30 cm^2 or less, a flux of at least about 100, more preferably at least about 200 $\mu g/cm^2/day$, androgenic agent must be achieved. The systems provided herein, and particularly those containing high capacity drug reservoirs, are effective to accomplish the foregoing.

In one embodiment, the invention involves the use of high capacity drug reservoirs which are polymeric hydrogel matrices, preferably polyurethane hydrogels. Generally, these hydrogel matrices are formed by admixing a polyurethane with a suitable crosslinking agent, in the presence of water. Drug formulation may be incorporated into the hydrogel during

hydrogel manufacture, i.e., admixed with the polyurethane along with the crosslinking agent and water, or it may be incorporated into the hydrogel after manufacture, i.e., after water is added.

Suitable polyurethanes useful for forming the hydrogel reservoir may be chemically synthesized using conventional techniques known to those skilled in the art or described in the pertinent literature. The polyurethanes can be polyurethane elastomers such as those available as Airthane®, Polathane®, Ultracast® and Cyanaprene® from Air Products and Chemicals Inc., as Conathane® from Conap, Inc., as Bayte C®, Baymidur Vul Kollan®, Baydur®, Bayflex® or Baygal® from Miles Inc., Polymers, Division; alternatively, polyurethane resins such as Desmodur® or Mondur® resins, which can be obtained from Miles, Inc., Industrial Chemicals Division, can be used. Hydrophilic polyurethane prepolymers such as those available under the Hypol® trademark from W.R. Grace & Co., Organic Chemicals Division, may be used as well, and are particularly preferred; and an example of a particularly effective commercially available polyurethane that can be used in conjunction with the present invention is Hypol® PreMA G-50 polymer, available from the Hampshire Chemical Corporation.

In order to form the hydrogel, as explained above, a crosslinking agent is added to the polyurethane in the presence of water. Preferred crosslinking agents are diisocyanates, including aliphatic, cycloaliphatic and aromatic diisocyanates. Suitable diisocyanates include, but are not limited to, tetramethylene diisocyanate, hexamethylene diisocyanate, trimethylene diisocyanate, trimethylhexamethylene diisocyanate, cyclohexyl-1,2-diisocyanate, cyclohexylene-1,4-diisocyanate, 2,4-toluene diisocyanate, and 2,6-toluene diisocyanate. The amount of crosslinking agent used will be such that it is effective to produce the desired hydrogel, but preferably less than that which would result in any unconsumed material. However, if excess crosslinking agent is present after hydrogel formation, it may be removed using a simple washing step.

Generally, the reaction mixture for forming the polyurethane hydrogel will contain about 5 wt.% to 25 wt.% isocyanate crosslinking agent and about 0.01 wt.% to 15 wt.% water, with the polyurethane representing the remainder of the composition, along with the drug formulation, if it is incorporated during manufacture. It will be appreciated by those skilled in the art, however, that the various components of the reservoir may need to be varied, e.g., depending on the degree of tack desired (which would in turn necessitating a higher fraction of water) or on some other desired characteristic of the final product.

The drug formulation may be incorporated into the hydrogel during hydrogel formation or subsequent thereto. Generally, the latter procedure is preferred, as a greater degree of drug may be incorporated into the hydrogel; that is, by absorbing drug into the hydrogel after the hydrogel is prepared, drug loading of as high as 65 wt.% to 70 wt.% or higher can be achieved.

In an alternative embodiment, a photocurable polyurethane is used at the outset, to form the hydrogel. In such a case, curing may be effected using radiation of a suitable wavelength, rather than a crosslinking agent. Photocuring can in some cases be neater, and done more rapidly, than curing using a diisocyanate-type crosslinking agent. With photocuring, it is typically necessary to carry out the curing step in the presence of a photoinitiator. Suitable photoinitiators are radical photoinitiators that are well known to those skilled in the art. Examples of such photoinitiators include α-alkoxy deoxybenzoins, α,α-dialkoxy deoxybenzoins, α,α-dialkoxy acetophenones, 2-hydroxy-2,2-dialkyl acetophenones, benzophenones, thioxanthones, benzils, and other compounds identified by H.J. Hageman et al., "Photoinitiators and Photocatalysts for Various Polymerisation and Crosslinking Processes," in Radiation Curing of Polymers II, ed. D.R. Randell (The Royal Society of Chemistry, 1991), at pp. 46-53.

In another embodiment, the high capacity drug reservoir is comprised of a superabsorbent material. The nature of the superabsorbent

material is not critical; it is, as noted earlier herein, the degree of absorbency that is important. Typically, crosslinked polymer and/or copolymer compositions are preferred such as poly(acrylates), poly(maleic anhydrides), poly(vinyl alcohols), poly(ethylene oxides), poly(hydroxy methylenes), polysaccharides, and the like, as described in Chen et al. (1985) *Synthetic and Natural Polymers*, in Chatterjee (Ed.) *Absorbency*, chapter VI, pp. 197-216 (Elsevier, Amsterdam). Specific examples of superabsorbent materials include but are not limited to the reaction product at elevated temperature and pressure of hydrolyzed starch polyacrylonitrile graft copolymer, optionally having added thereto a polyhydric alcohol such as glycerol (*see*, *e.g.*, U.S. Patent Nos. 4,467,012 and 4,412,036 to Pedersen et al.), a polymer network of a crosslinked polyurethane that is prepared from an isocyanate-terminated poly(oxyalkylene)polyol and a substantially linear addition polymer containing functional groups selected from the group consisting of carbamoyl, substituted carbamoyl and carboxy, and the alkali metal and ammonium salts thereof, the chemical structure and preparation of which is described in U.S. Patent No. 4,731,391 to Garvey, a skeletal network of a cellular polymer, preferably polyurethane, foam containing a superabsorbent material such as carboxymethyl cellulose, starch-grafted sodium polyacrylate and sodium polyacrylate as disclosed in U.S. Patent No. 4,985,467 to Kelly et al., or a superabsorbent crosslinked ampholytic ion pair copolymer, for example, the ammonium cation 3-methacrylamidopropyltrimethylammonium and a sulfonate anion such as sulfonate, 2-methylacryloyloxyethane sulfonate, vinyl sulfonate, styrene sulfonate, or the like, as disclosed in U.S. Patent No. 5,216,098 to Ahmed et al. Other such superabsorbent materials are well known to those of ordinary skill in the art. Preferably, the superabsorbent material an olefin/alkyl carboxylate copolymer, more preferably the superabsorbent material is a maleic anhydride-isobutylene copolymer (as may be obtained as Fiberdri® superabsorbent fibers from Camelot Superabsorbents Incorporated, Charlotte, NC). A superabsorbent film comprising such a copolymer may be obtained from Concert Industries Limited (Thurso, Quebec, Canada).

The reservoir layer will generally although not necessarily range in thickness from about 1 to about 100 mils, preferably in the range of approximately 25 to 60 mils. It will be appreciated that the thickness of the reservoir will depend, however, on the type of reservoir employed as well as on a variety of other considerations, including the quantity of drug to be incorporated in the reservoir, desired patch size, and the like.

Androgenic agents which may be delivered using the methods, reservoirs and systems of the invention generally include, but are not limited to, the following: the naturally occurring androgens androsterone and testosterone; pharmaceutically acceptable esters of testosterone, typically esters formed from the hydroxyl group present at C-17, and particularly the enanthate, propionate, cypionate and phenylacetate esters; and pharmaceutically acceptable derivatives of testosterone such as methyltestosterone, testolactone, oxymetholone and fluoxymesterone. Testosterone and the 17-esters thereof, particularly the enanthate, propionate and cypionate esters, are preferred.

Other pharmaceutically active agents, particularly additional steroidal agents, may be administered along with the selected androgenic agent. These agents will generally be estrogens and/or progestogens. Examples of estrogens include, but are not limited to, estradiol and its esters (e.g., estradiol benzoate, valerate, cyprionate, decanoate and acetate), ethynyl estradiol, estriol, estrone and mestranol; examples of progestogens include flurogestone acetate, hydroxyprogesterone, hydroxyprogesterone acetate, hydroxyprogesterone caproate, medroxyprogesterone acetate, norethindrone, norethindrone acetate, norethisterone, norethynodrel, desogestrel, 3-keto desogestrel, gestadene and levonorgestrel.

The amount of each such additional agent incorporated into the drug reservoir will vary, depending on the intended dosage, which in turn will vary with the individual being treated, the particular indication, and the like. Normally, the daily dosage of estrogenic agent will be at least about 0.03 mg/day, while the daily dosage of progestogen will be at least about 0.2

mg/day, depending, of course, on the particular estrogen and progestogen to be administered.

It will generally be preferred to administer androgenic agents as provided herein in conjunction with a permeation enhancer. Suitable enhancers include, but are not limited to, dimethylsulfoxide (DMSO), dimethyl formamide (DMF), N,N-dimethylacetamide (DMA), decylmethylsulfoxide (C_{10}MSO), polyethylene glycol monolaurate (PEGML), propylene glycol (PG), propylene glycol monolaurate (PGML), glycerol monolaurate (GML), methyl laurate (ML), lauryl lactate (LL), methyl decanoate (MD), isopropyl myristate (IPM), terpenes such as menthone, C_2-C_6 alkanediols, particularly 1,2-butanediol (BD), lecithin, the 1-substituted azacycloheptan-2-ones, particularly 1-n-dodecyl-cyclazacycloheptan-2-one (available under the trademark Azone® from Whitby Research Incorporated, Richmond, VA), alcohols, and the like. Vegetable oil permeation enhancers, such as described in U.S. Patent No. 5,229,130 to Sharma, assigned to Cygnus, Inc. (Redwood City, California) may also be used. Such oils include, for example, safflower oil, cotton seed oil and corn oil.

One group of preferred enhancers for use in conjunction with the transdermal administration of androgenic agents are esters given by the formula $[CH_3(CH_2)_mCOO]_nR$ in which m is an integer in the range of 8 to 16, n is 1 or 2, and R is a lower alkyl (C_1-C_3) residue that is either unsubstituted or substituted with one or two hydroxyl groups. In the preferred embodiment herein, the ester component is a lower alkyl (C_1-C_3) laurate (i.e., m is 10 and n is 1), and in a particularly preferred case is "PGML." It will be appreciated by those skilled in the art that the commercially available material sold as "PGML" is typically a mixture of propylene glycol monolaurate itself, propylene glycol dilaurate, and either propylene glycol, methyl laurate, or both. Thus, the terms "PGML" or "propylene glycol monolaurate" as used herein are intended to encompass both the pure compound as well as the mixture that is typically obtained commercially.

Also preferred are fatty acids and fatty alcohols corresponding to the above-defined fatty esters. Thus, fatty acids useful as permeation enhancers herein will generally have the formula $CH_3(CH_2)_mCOOH$, where m is as above, while the fatty alcohols will have the formula $CH_3(CH_2)_mCH_2OH$.

Other preferred enhancer compositions are wherein a fatty ester as described above is combined with an ether component selected from the group consisting of diethylene glycol monoethyl ether and diethylene glycol monomethylether. Such enhancer compositions are described in detail in U.S. Patent Nos. 5,053,227 and 5,059,426 to Chiang et al. (assigned to Cygnus, Inc., Redwood City, California).

Particularly preferred permeation enhancers are selected from the group consisting of C_2-C_6 alkanediols, fatty esters having the structural formula $[CH_3(CH_2)_mCOO]_nR$, fatty acids having the structural formula $CH_3(CH_2)_mCOOH$, fatty alcohols having the structural formula $CH_3(CH_2)_mCH_2OH$, and mixtures thereof, where m and n are as defined above. It has been found that ternary vehicle combinations in which such a fatty alcohol or acid is combined with a fatty ester and a C_2-C_6 alkanediol, are particularly effective enhancer compositions for use in conjunction with the present invention.

The amount of enhancer present in the composition will similarly depend on a number of factors, e.g., the strength of the particular enhancer, the desired increase in skin permeability, rate of administration, and amount of drug delivered.

Preferred compositions, unless incorporated into a drug delivery system as described below, will typically contain on the order of about 0.01 wt.% to 10 wt.% drug formulation, and about 1.0 wt.% to 20.0 wt.% enhancer, with the remainder of the composition being either a liquid or polymeric carrier (including optional additives as outlined above). The enhancer portion of the composition may contain a single enhancer or it may be a mixture of enhancers.

It will be appreciated by those skilled in the art that any number of patch configurations may be used in conjunction with the present androgen-containing high capacity drug reservoirs; the following structures are described by way of example only, and are not intending to be limiting.

Generally, although not necessarily, a backing layer is laminated to the hydrogel or superabsorbent reservoir following reservoir preparation. The backing layer functions as the primary structural element of the device and provides the device with much of its flexibility, drape and, preferably, occlusivity. The material used for the backing layer should be inert and incapable of absorbing drug, enhancer or other components of the pharmaceutical composition contained within the device. The backing is preferably made of one or more sheets or films of a flexible elastomeric material that serves as a protective covering to prevent loss of drug and/or vehicle via transmission through the upper surface of the device, and will preferably impart a degree of occlusivity to the device, such that the area of the skin covered on application becomes hydrated. The material used for the backing layer should permit the device to follow the contours of the skin and be worn comfortably on areas of skin such as at joints or other points of flexure, that are normally subjected to mechanical strain with little or no likelihood of the device disengaging from the skin due to differences in the flexibility or resiliency of the skin and the device. Examples of materials useful for the backing layer are polyesters, polyethylene, polypropylene, polyurethanes and polyether amides. The layer is preferably in the range of about 15 microns to about 250 microns in thickness, and may, if desired, be pigmented, metallized, or provided with a matte finish suitable for writing.

Underneath the reservoir, i.e., on the "skin" side thereof, may be a pharmaceutically acceptable contact adhesive for affixing the device to the skin during drug delivery. With hydrogels or superabsorbent materials which adhere well to the skin or mucosal tissue, use of a contact adhesive is unnecessary. Most hydrogels or superabsorbent materials, however, will not adhere sufficiently, and a contact adhesive or some other means for

maintaining the system in drug transmitting relationship to the skin is required. If a contact adhesive is used, it may be in the form of a layer which covers the entire drug reservoir, thus serving as the basal surface of the device during use (in which case it may be necessary to enhance the porosity of the adhesive material to allow drug to penetrate therethrough), or it may be in the form of a peripheral ring. Suitable contact adhesive materials are pressure-sensitive adhesives suitable for long-term skin contact, which are also be physically and chemically compatible with the drug formulation, i.e., the drug itself and any carriers and vehicles employed. It is essential that the contact adhesive not comprise a drug-absorbent material, as such a material would inhibit drug flux. Preferred materials for this layer include, for example, polysiloxanes, polyisobutylenes, polyacrylates, polyurethanes, plasticized ethylene-vinyl acetate copolymers, low molecular weight polyether amide block polymers (e.g., PEBAX), tacky rubbers such as polyisobutene, polystyrene-isoprene copolymers, polystyrene-butadiene copolymers, and mixtures thereof.

It may also be desirable to include a rate-controlling membrane in between the drug reservoir and a contact adhesive layer, when one is present. Representative materials useful for forming rate-controlling membranes include polyolefins such as polyethylene and polypropylene, polyamides, polyesters, ethylene-ethacrylate copolymer, ethylene-vinyl acetate copolymer, ethylene-vinyl methylacetate copolymer, ethylene-vinyl ethylacetate copolymer, ethylene-vinyl propylacetate copolymer, polyisoprene, polyacrylonitrile, ethylene-propylene copolymer, and the like. Generally, a preferred material useful to form the rate-controlling membrane is ethylene-vinyl acetate copolymer. The particular material selected will be such that the flux of drug component or of one or more non-drug components, i.e., will be controlled as desired.

Additionally, to protect the basal surface of the device during storage and just prior to use, a release liner is provided to cover the exposed reservoir or adhesive surface. The release liner is a disposable element,

typically formed from a material impermeable to the drug, vehicle and adhesive, and which is easily stripped from the contact adhesive. Release liners are typically treated with silicone or fluorocarbons. Silicone-coated polyester is presently preferred.

An example of a laminated composite containing a high capacity drug reservoir of the invention is shown in FIG. 1. The composite is generally designated **10**, and comprises a backing layer **11**, drug reservoir **12** containing drug **12a**, optional rate-controlling membrane **13**, optional contact adhesive layer **14**, and a release liner **15**. In an alternative embodiment, the adhesive may be present as a peripheral ring rather than as an "in-line" layer.

Alternative drug delivery systems may be used as well, as will be appreciated by those skilled in the art of transdermal drug administration. One such system is substantially as described above and as shown in FIG. 1, but reservoir layer **12** comprises a matrix of a continuous hydrophobic polymer phase, with a particulate phase of a hydrated inorganic silicate and drug adsorbed or absorbed thereby (see PCT Publication No. WO94/07468, entitled "Two-Phase Matrix for Sustained Release Drug Delivery Device"). Polymers which may be used as the continuous hydrophobic phase are polysiloxanes, polyisobutylene, solvent-based hydrophobic polyacrylates, polyurethanes, plasticized ethylene-vinyl acetate copolymers, low molecular weight polyether block amide copolymers, styrene-butadiene polymers, and vinyl acetate-based adhesives, with the hydrophobic polymer normally constituting about 30 wt.% to 95 wt.%, more typically 40 wt.% to 60 wt.%, of the matrix. The dispersed inorganic silicate is in the form of particulates that are typically in the non-colloidal size range of 0.001 to 0.1 mm, more usually 0.01 to 0.05 mm.

Preferably, the matrix in such an embodiment additionally contains a dispersing agent which aids in maintaining the particulate phase dispersed in the continuous phase. Anionic, cationic, amphoteric or nonionic dispersing agents may be used. Preferably, the dispersing agent is a non-ionic surfactant such as a polyethylene-polyoxypropylene glycol copolymer (e.g.,

that sold under the "Pluronic" trademark) or a polyoxyethylene sorbitan ester (e.g., that sold under the "Tween" trademark); the dispersing agent will normally constitute about 0.5 wt.% to 10 wt.% of the matrix, more usually 3 wt.% to 6 wt.% of the matrix.

These matrices are prepared by dissolving the drug in water (with, optionally, additional hydrophilic polar solvents) and contacting the hydrophilic particulate material with the resulting solution to permit the aqueous solution to be absorbed by the particulate material. The mixture will typically have the texture of a paste. The hydrophobic components of the matrix and the dispersing agent, preferably in admixture, are added to the paste with vigorous mixing to form a viscous dispersion. This dispersion may be formed into appropriate shapes and excess solvent removed therefrom.

FIG. 2 depicts an alternative device structure for administering a drug transdermally. The device is a "liquid reservoir" type and is generally designated **16**. It comprises a top, impermeable backing layer **17**, an underlying liquid, gel or foam layer **18**, generally a liquid layer, containing the drug and any associated materials, e.g., enhancers or the like, that is sealed at its edge to the overlying backing layer to form a pouch between the backing and the underlying modulator layer **19**, and a pressure-sensitive adhesive layer **20** that serves as the basal surface of the device and affixes the device to the skin during use. The modulator layer is generally a thin, flexible layer of a highly porous material such as polyester, polyethylene, polypropylene, or the like (it should be noted, however, that when layer **18** is a gel or foam, the modulator layer is optional). Prior to use, the device is provided with a release liner (not shown) to protect adhesive layer **20** prior to use.

Transdermal drug delivery systems for use in conjunction with the invention are fabricated as described herein or using conventional techniques which are within the skill of the art, and/or explained in the literature.

The invention thus provides methods and systems for administering androgenic agents such as testosterone and derivatives thereof, alone or in combination with one or more estrogens and/or progestogens, at a high flux using a relatively small patch, on the order of 30 cm^2 or less.

It is to be understood that while the invention has been described in conjunction with the preferred specific embodiments thereof, that the description above as well as the examples which follow are intended to illustrate and not limit the scope of the invention. Other aspects, advantages and modifications within the scope of the invention will be apparent to those skilled in the art to which the invention pertains.

In the following examples, efforts have been made to ensure accuracy with respect to numbers used (e.g., amounts, temperature, etc.) but some experimental error and deviation should be accounted for. Unless indicated otherwise, temperature is in degrees C and pressure is at or near atmospheric.

Experimental

Materials:

Testosterone was purchased from Sigma Chemical Company and used as received. All chemicals used were of reagent grade.

Solubility Determination:

The solubilities of testosterone in various vehicles or the combinations of vehicles were determined. An excess amount of testosterone was added to the vehicles and stirred overnight in an incubator at 32°C. Saturated solutions of testosterone were obtained after filtration of the excess testosterone. Samples were diluted for HPLC assay.

Preparation of Liquid Vehicles:

Liquid vehicles were formulated on a weight basis. Testosterone was added to the vehicles in excess or at a known amount rotated overnight, filtered and the resultant liquid formulations were applied to the skin. Non-woven materials (Reemay) were used as a support for the liquid formulations.

Assay Methodology:

Samples were analyzed by HPLC (Perkin-Elmer) using the method described below:

Mobile phase: 48% acetonitrile:52% water
Flow rate: 1.0 ml/min
Diode array detector was set at 245 nm wavelength.

The column was Brownlee RP-18 (100 x 4.6mm) at 5 μm particle size.
Temperature: ambient
Testosterone retention time: about 4 min.

Preparation of Transdermal Systems:

Preparation of superabsorbent reservoir containing testosterone: Testosterone was dissolved in selected vehicle combinations as indicated in Tables 1 through 4. A superabsorbent material was absorbed with a combination of liquid vehicles and then applied to the skin as 1/2 inch diameter disks.

Preparation of Hydrogel Formulation: The prepolymer was mixed with the vehicle combinations and water. The mixture was left for 30 minutes to form a hydrogel. a 5/8 inch diameter disk of the gel was cut and put on the skin for the permeation studies.

In Vitro Skin Permeation Experiments:

Skin preparation: The skin permeation studies were performed with human cadaver skin. The epidermis was physically separated from the dermis of dermatomed split-thickness cadaver skin following a two-minute immersion in water heated to 60°. The stored epidermis was thawed, tested for leaks and used for skin permeation studies.

Permeation study: Franz cells with a diffusional area of 0.71 cm^2 and a receiver volume of 7.5 ml were used. Saline solution containing 2% (w/v) hydropropyl-β-cyclodextrin was used as the receiver fluid. The heat-separated epidermis was mounted on the diffusion cell with the stratum corneum facing the donor compartment. Liquid formulations were added to the donor compartment. Non-woven fabric (Reemay) punched into 5/8 inch

diameter disks was used to support the stratum corneum. For the superabsorbent formulations, the superabsorbent was cut into 1/2 inch diameter disk and mounted directly on the skin. The hydrogel system was applied onto the stratum corneum prior to mounting on the diffusion cell. At pre-determined time periods, samples were taken from the receiver cell and analyzed by HPLC. The total volume of the receiver cell was replaced with fresh fluid.

Several sets of skin flux experiments were conducted. The total amount of testosterone delivered through the skin and the flux of testosterone versus time were calculated.

The binary vehicles tested provided steady-state fluxes in the range of 4-10 $\mu g/cm^2/hr$ over the 24 hour time period (Table 1). Even though a 3-10 fold increase was observed in comparison to PGML, the flux was still lower than expected. A series of ternary vehicles with fatty acids or alcohols, fatty acid esters and solvents were studied. With these ternary solvent combinations, the flux of testosterone and cumulative permeation exhibited the desired phasic profiles (FIGS. 3, 4 and 5). The solubilities of testosterone in these vehicles are listed in Tables 2 and 3.

A skin flux study was conducted to evaluate the fluxes of testosterone from the gel and superabsorbent designs. Again, the flux of testosterone from the superabsorbent and gel platforms all exhibited the desired phasic profiles (FIG. 6). With a ternary vehicle and superabsorbent design, the testosterone delivered at 24 hr was about 250 $\mu g/cm^2$ (Table 4 and FIG. 7).

Table 1
Testosterone Skin Flux from Binary Vehicles

Vehicles	Skin Flux ($\mu g/cm^2/hr$)	Solubility (mg/ml)
PGML:PG (10:90)	10.5±3.6	92.8
Methyl Laurate:PG (50:50)	7.3±0.5	108.5
Oleyl Alcohol:PG (10:90)	7.3±0.8	87.9
Oleyl Alcohol:PG (50:50)	6.8±0.3	102.6
Oleic Acid:PG (3:97)	11.1±2.8	65.5
Isopropyl Myristate:PG (50:50)	6.1±0.8	13.3
PGML:1,2-Butanediol (25:75)	11.5±3.7	59.2
Isopropyl Palmitate:PG (50:50)	4.7±0.5	9.9
PGML	1.3±0.1	69.0

*All formulations were saturated with testosterone.

Table 2
Solubility of Testosterone in Ternary Vehicles

Formulation #	Vehicles	Solubility (mg/ml)
1.	Oleic Acid:Methyl Laurate:PG (10:45:45)	63.7
3.	Oleic Acid:Methyl Laurate:1,2-Butanediol (10:45:45)	113.0
4.	Oleic Acid:PGML:1,2-Butanediol (10:45:45)	102.1
5.	Oleic Acid:Methyl Laurate:transcutol (10:45:45)	73.0
6.	Oleyl Alcohol:Methyl Laurate:PG (10:45:45)	54.6
7.	Oleyl Alcohol:PGML:1,2-Butanediol (10:45:45)	113.5
8.	Benzyl Alcohol:PGML:1,2-Butanediol (10:45:45)	156.7
9.	PGML	69.0

Table 3
Solubility of Testosterone in Ternary Vehicles

Formulation #	Vehicles	Solubility (mg/ml)
1.	Oleyl Alcohol:PGML:1,2-Butanediol (10:45:45)	119.7
2.	Oleyl Alcohol:PGML:1,2-Butanediol (45:40:15)	80.9
3.	Oleyl Alcohol:PGML:1,2-Butanediol (40:30:30)	112.5
4.	Lauric Acid:Methyl Laurate:1,2-Butanediol (20:40:40)	127.3
5.	Lauric Acid:PGML:1,2-Butanediol (20:40:40)	126.5
6.	Oleyl Alcohol:PGML:PG (10:45:45)	83.4
7.	Benzyl Alcohol:Methyl Decanoate:1,2-Butanediol (20:40:40)	241.2
8.	Lauryl Alcohol:Methyl Laurate:1,2-Butanediol (20:40:40)	127.5
9.	Lauryl Alcohol:Methyl Laurate:PG (20:40:40)	138.4

Table 4
Cumulative Permeation of Testosterone
from Platforms at 24 Hours

Formulation #	Platform	Om ($\mu g/cm^2$)
1.	Super Absorbent (Lauric Acid:ML:BD 20:40:40)	249±47
2.	Hydrogel (Lauric Acid:ML:BD 20:40:40)	198±74
3.	Super Absorbent (Lauryl Alcohol:ML:BD 20:40:40)	150±9
4.	Hydrogel (Lauryl Alcohol:ML:BD 20:40:40)	127±58
5.	Super Absorbent (Benzyl Alcohol:MD:BD 20:40:40)	162±11
6.	Hydrogel (Benzyl Alcohol:MD:BD 20:40:40)	181±28

Claims:

1. A transdermal drug delivery system for administering an androgenic agent to an individual in need of such therapy, comprising a laminated composite of:

a drug reservoir containing a predetermined quantity of a pharmaceutical formulation in which an androgenic agent is present at or above saturation; and

a backing layer that is substantially impermeable to the drug and which defines the upper surface of the system during drug delivery.

2. The system of claim 1, wherein the drug reservoir is a high capacity drug reservoir.

3. The system of claim 2, wherein the high capacity drug reservoir is comprised of a material effective to provide a flux of androgenic agent of at least about 100 $\mu g/cm^2/day$.

4. The system of claim 3, wherein the high capacity drug reservoir is comprised of a material effective to provide a flux of androgenic agent of at least about 200 $\mu g/cm^2/day$.

5. The system of claim 3, wherein the high capacity drug reservoir is comprised of a polyurethane hydrogel.

6. The system of claim 3, wherein the high capacity drug reservoir is comprised of a superabsorbent material capable of absorbing an amount of pharmaceutical formulation corresponding to more than 15 grams formulation per gram of superabsorbent material.

7. The system of claim 6, wherein the superabsorbent material is selected from the group consisting of poly(acrylates), poly(maleic anhydrides), poly(vinyl alcohols), poly(ethylene oxides), poly(hydroxy methylenes), polysaccharides and olefin/alkyl carboxylate copolymers.

8. The system of claim 1, wherein the androgenic agent is selected from the group consisting of androsterone, testosterone, methyl testosterone, testolactone, oxymetholone, fluoxymesterone, pharmaceutically acceptable C-17 esters of testosterone, and mixtures thereof.

9. The system of any one of claims 1, 5 or 6, wherein the pharmaceutical formulation further comprises an additional steroidal agent selected from the group consisting of estrogens, progestogens, and combinations thereof.

10. The system of any one of claims 1, 5 or 6, wherein the pharmaceutical formulation further comprises a skin permeation enhancer composition.

11. The system of claim 10, wherein the skin permeation enhancer composition comprises: (a) a first component selected from the group consisting of fatty acids of the formula $CH_3(CH_2)_mCOOH$ and fatty alcohols of the formula $CH_3(CH_2)_mCH_2OH$, where m is an integer in the range of 8 to 16; (b) a second component comprising a fatty ester $[CH_3(CH_2)_mCOO]_nR$ in which m is an integer in the range of 8 to 16, n is 1 or 2, and R is a lower alkyl (C_1-C_3) residue that is either unsubstituted or substituted with one or two hydroxyl groups; and (3) a third component comprising a C_2-C_6 alkanediol.

12. The system of any one of claims 1, 5 or 6, further including a maintaining means for affixing the system to the skin or mucosal tissue during drug delivery.

13. The system of claim 12, wherein the maintaining means comprises a layer of a pharmaceutically acceptable contact adhesive laminated to the reservoir which serves as the basal surface of the system during drug delivery.

14. The system of claim 12, wherein the maintaining means comprises a peripheral ring of a pharmaceutically acceptable contact adhesive present on the reservoir.

15. The system of any one of claims 1, 5 or 6, wherein the drug reservoir contains at least about 40 wt.% pharmaceutical formulation.

16. The system of any one of claims 1, 5 or 6, wherein the drug reservoir contains at least about 65 wt.% pharmaceutical formulation.

17. The system of any one of claims 1, 5 or 6, further including a rate-controlling membrane disposed between the drug reservoir and the contact adhesive layer.

18. A reservoir for incorporation into a transdermal drug delivery system useful for administering an androgenic agent transdermally, comprising a polyurethane hydrogel containing a pharmaceutical formulation in which an androgenic agent is present therein at or above saturation.

19. A reservoir for incorporation into a transdermal drug delivery system useful for administering an androgenic agent transdermally,

comprising a superabsorbent material containing a pharmaceutical formulation in which an androgenic agent is present therein at or above saturation.

20. A method for administering an androgenic agent to an individual in need of such therapy, comprising administering to the individual a selected androgenic agent, or a pharmaceutically acceptable ester thereof, through a predetermined area of intact skin at an administration rate sufficient to provide a therapeutically effective blood level of agent, wherein the agent is administered from a transdermal drug delivery system comprising a drug reservoir containing a pharmaceutical formulation in which the androgenic agent is present at or above saturation.

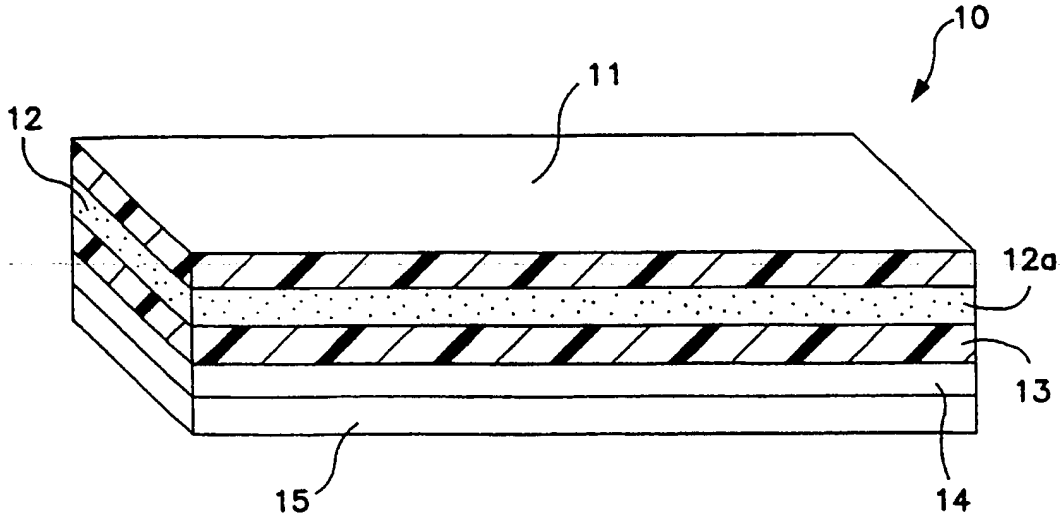


FIG. 1

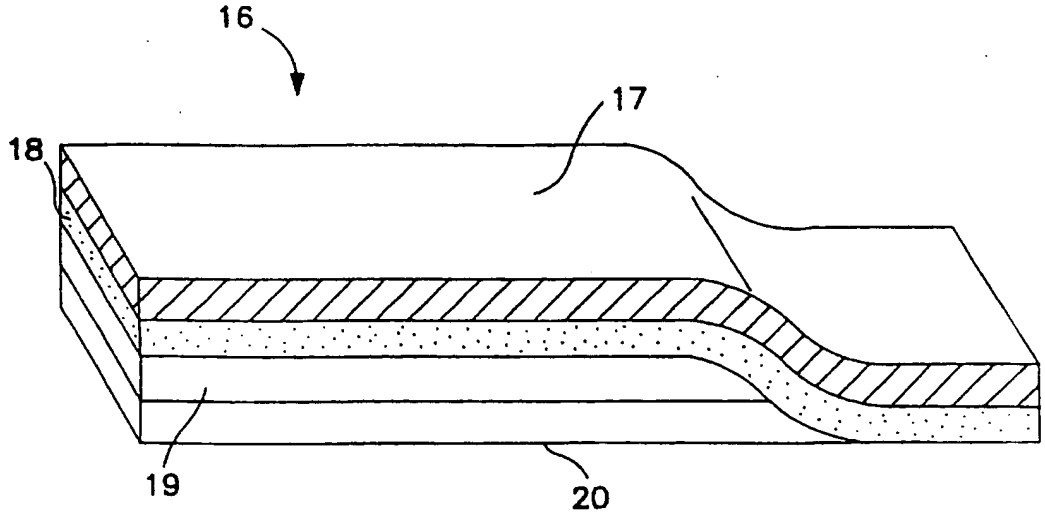


FIG. 2

FIG. 3

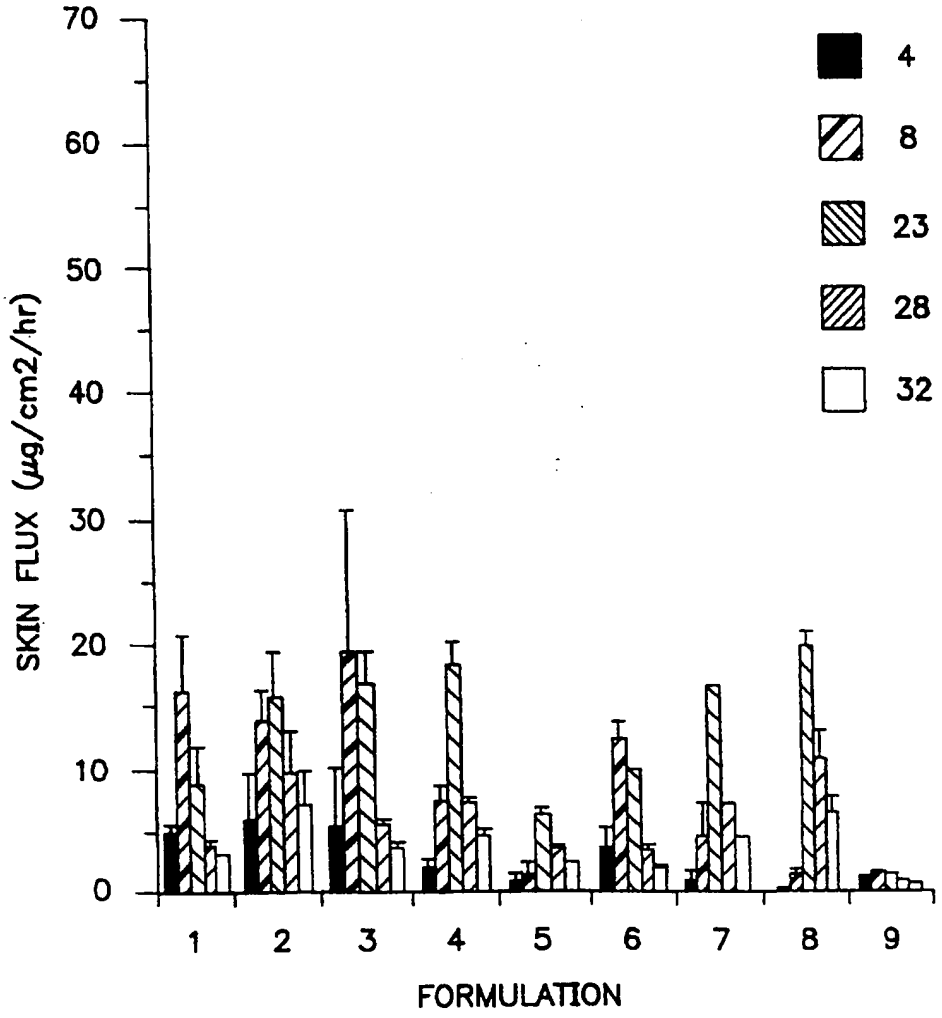

70
60
50
40
30
20
10
0
SKIN FLUX (µg/cm2/hr)
1
2
3
4
5
6
7
8
9
FORMULATION
4
8
23
28
32

FIG. 4

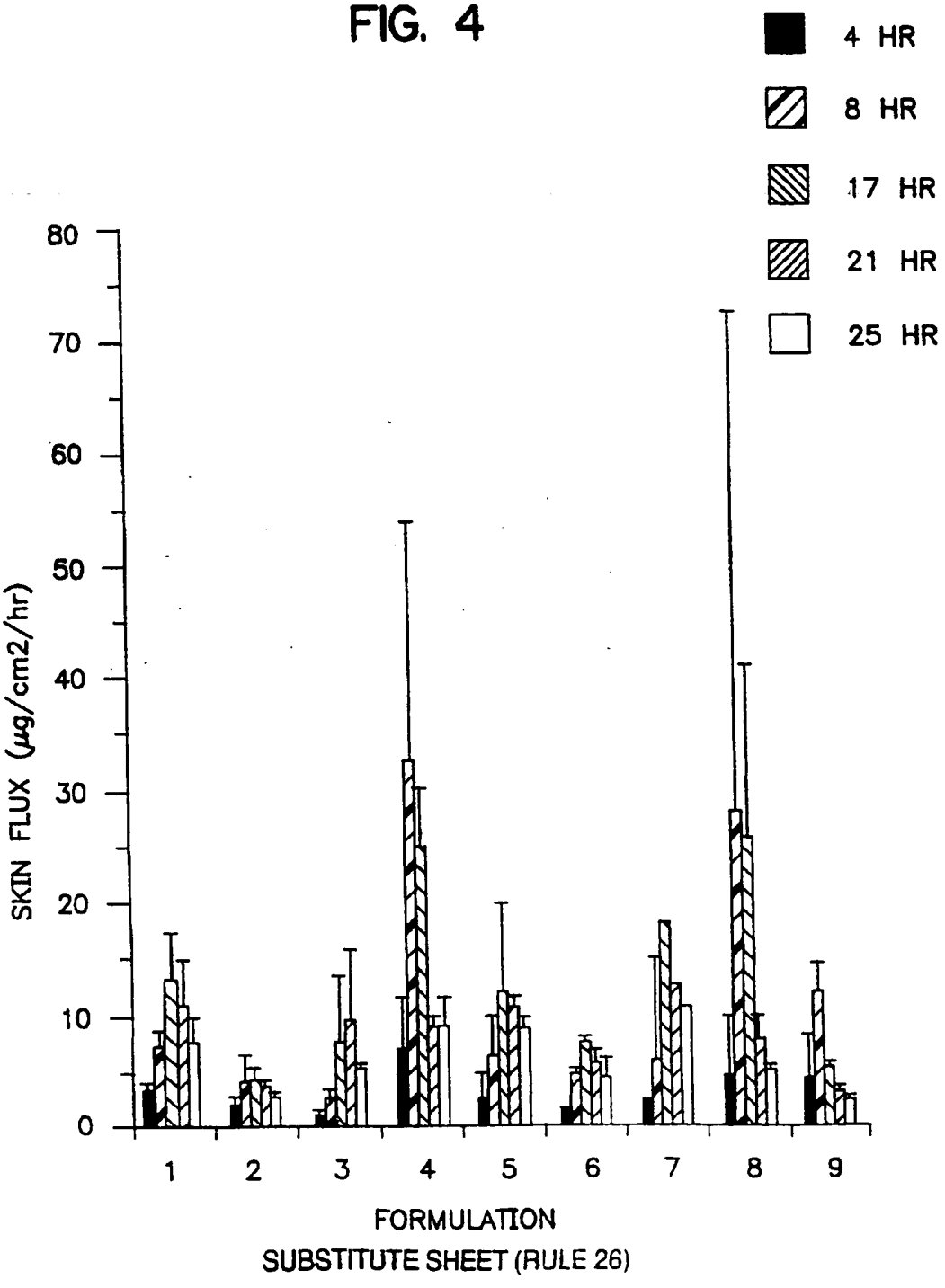

4 HR
8 HR
17 HR
21 HR
25 HR
SKIN FLUX (µg/cm2/hr)
0
10
20
30
40
50
60
70
80
1
2
3
4
5
6
7
8
9
FORMULATION

FIG. 5

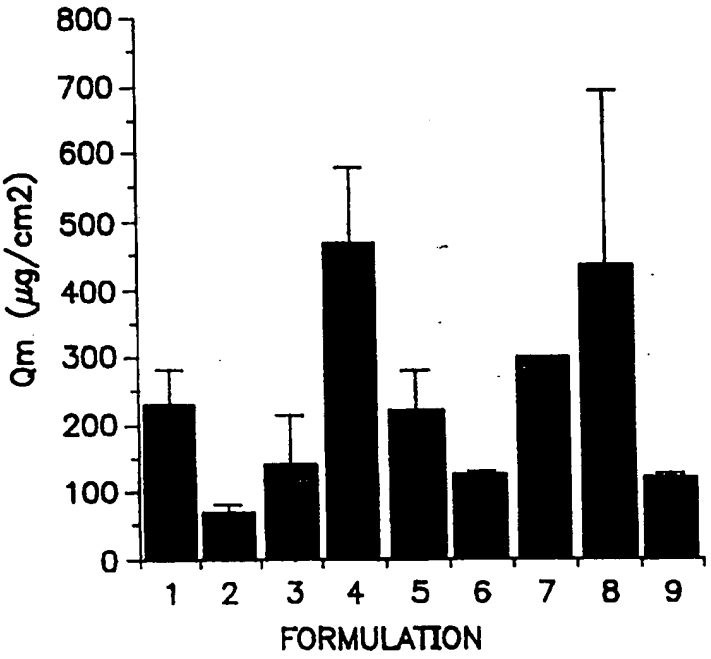

800
700
600
500
400
300
200
100
0
Qm (μg/cm2)
1
2
3
4
5
6
7
8
9
FORMULATION

FIG. 6

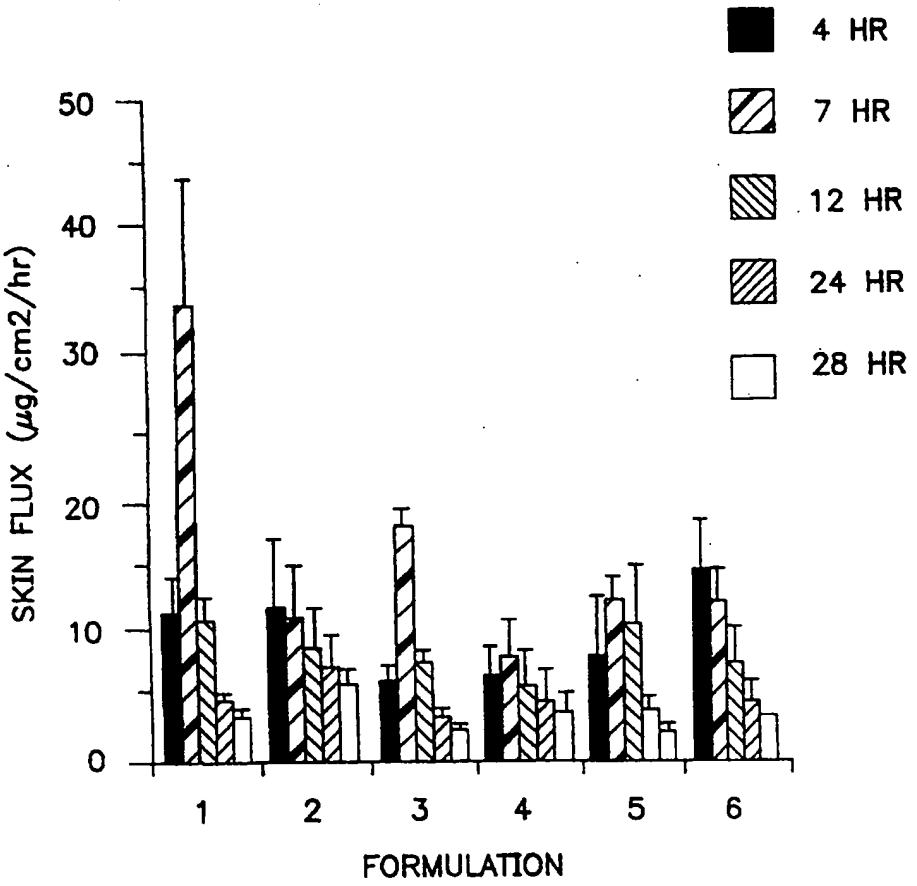
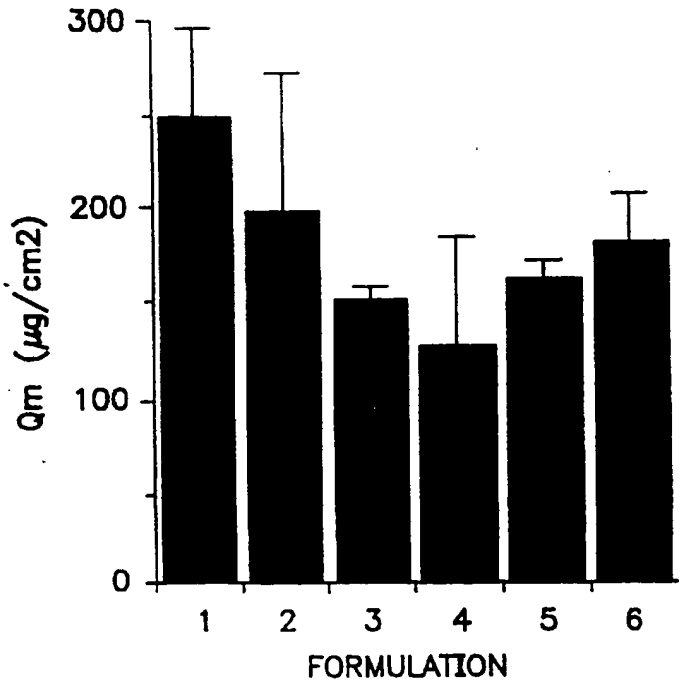

4 HR
7 HR
12 HR
24 HR
28 HR
SKIN FLUX (µg/cm2/hr)
50
40
30
20
10
0
1
2
3
4
5
6
FORMULATION

FIG. 7



INTERNATIONAL SEARCH REPORT

Int ional Application No
PCT/US 96/20365

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61L15/44

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 09006 A (ALZA CORP ;TASKOVICH LINA TORMEN (US); YUM SU IL (US); LEE EUN SOO) 6 April 1995 see page 28 - page 30; example 6 see page 13, line 14 - line 20 ---	1,3,4,8, 10, 12-14,20
X	WO 94 06383 A (UNIV RUTGERS) 31 March 1994 see page 52 - page 54; example 2 ---	1-4, 7-10,12, 13,19,20
X	US 4 863 970 A (PATEL DINESH C ET AL) 5 September 1989 see column 10, line 64 see column 12 - column 13; example 4 --- -/--	1,3,4,8, 10,20

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

1

Date of the actual completion of the international search
29 May 1997

Date of mailing of the international search report
09.06.97

Name and mailing address of the ISA
European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+ 31-70) 340-3016

Authorized officer
Boulois, D

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 96/20365

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 564 364 A (ZAFFARONI ALEJANDRO ET AL) 14 January 1986 see column 12; example 2 see claim 1	1,8,20
E	WO 97 09971 A (CYGNUS THERAPEUTIC SYSTEMS ;CHEN TUNG FEN (US); CHIANG CHIA MING () 20 March 1997 see page 19, line 26 - line 28 see page 28 - page 29; example 3	1-4,6-20
E	WO 97 09970 A (CYGNUS THERAPEUTIC SYSTEMS ;CHEN TUNG FEN (US); CHIANG CHIA MING () 20 March 1997 see page 19, line 12 - page 22, line 2 see page 23, line 17 - line 33 see page 28 - page 29; example 3	1-6, 8-16, 18-20
P,X	WO 96 35427 A (HEXAL AG ;FISCHER WILFRIED (DE); BRACHER DANIEL (DE)) 14 November 1996 see page 9	1,2,6-8, 10, 12-14, 19,20
A	EP 0 399 432 A (TAKEDA CHEMICAL INDUSTRIES LTD) 28 November 1990 see claims 1,8	1-20
A	JOURNAL OF CONTROLLED RELEASE, vol. 29, no. 1/02, 1 February 1994, pages 177-185, XP000433662 KENJU SUGIBAYASHI ET AL: "POLYMERS FOR TRANSDERMAL DRUG DELIVERY SYSTEMS" see page 178; table 1	1-20

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 96/20365

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Arucle 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim(s) 20 is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 1,3,4,20
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

See next page.

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant s protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US 96/ 20365

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

In view of the large number of compounds which are theoretically defined by the expression "androgenic agent" in Claims 1,3,4 and 20, the search has been restricted for economic reasons. The search was limited to the general concepts of "androgenic agent", to the compounds cited in th examples and claimed in Claim 8, and to the corresponding IPC classes (PCT Search Guidelines PCT/GL2, Chapter III, 2.1, 3.6 and 3.7).

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int ional Application No
PCT/US 96/20365

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9509006 A	06-04-95	AU 7924994 A	18-04-95
		AU 7964794 A	18-04-95
		CA 2165802 A	06-04-95
		CA 2167526 A	06-04-95
		EP 0721348 A	17-07-96
		EP 0721349 A	17-07-96
		NZ 274711 A	26-11-96
		NZ 275615 A	26-11-96
		WO 9509007 A	06-04-95
WO 9406383 A	31-03-94	AU 4923493 A	12-04-94
		CN 1092287 A	21-09-94
		EP 0616514 A	28-09-94
US 4863970 A	05-09-89	DE 3779999 A	30-07-92
		EP 0267617 A	18-05-88
		ES 2042527 T	16-12-93
		JP 63211241 A	02-09-88
		KR 9601373 B	27-01-96
US 4564364 A	14-01-86	AU 558500 B	29-01-87
		AU 2717284 A	29-11-84
		CA 1227982 A	13-10-87
		EP 0127282 A	05-12-84
		JP 60000822 A	05-01-85
WO 9709971 A	20-03-97	NONE	
WO 9709970 A	20-03-97	NONE	
WO 9635427 A	14-11-96	DE 19517145 C	28-11-96
		AU 5805096 A	29-11-96
EP 0399432 A	28-11-90	AT 107517 T	15-07-94
		CA 2017442 A	25-11-90
		DE 69010076 D	28-07-94
		DE 69010076 T	08-12-94
		JP 3072416 A	27-03-91
		US 5362497 A	08-11-94